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(71) Applicants: THE JOHNS HOPKINS UNIVERSITY [US/US]; 720 Rutland Avenue, Baltimore, MD 21205 (US). UTRECHT UNIVERSITY [NL/NL]; Heidelberglaan 100, NL-3584 CX Utrecht (NL).

(72) Inventors: BARKER, Nick; Parkstraat II, NL-3581 PB Utrecht (NL). CLEVERS, Hans; Ruysdaellaan 7, NL-3712 AP Huis ter Heide (NL). KINZLER, Kenneth, W.; 1403 Halkirk Way, Belair, MD 21015 (US). KORINEK, Vladimir; Kaplicka 49/856, 140 000 Prague 4 (CZ). MORIN, Patrice, J.; 10335 G Malcolm Circle, Columbia, MD 21030 (US). SPARKS, Andrew, B.; 10 Breton Hill Road – 3A, Baltimore, MD 21208 (US). VOGELSTEIN, Bert; 3700 Breton Way, Baltimore, MD 21208 (US).

(74) Agents: KAGAN, Sarah, A. et al.; Banner & Witcoff, Ltd., 11th floor, 1001 G Street, N.W., Washington, DC 20001-4597 (US).

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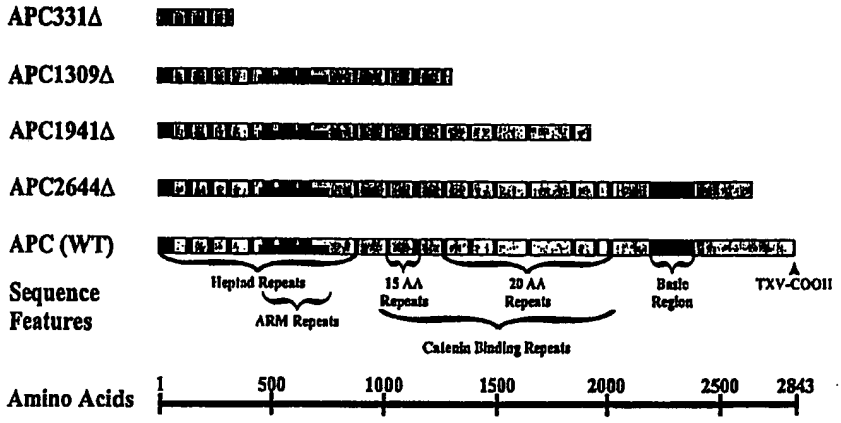

(57) Abstract

The APC tumor suppressor protein binds to β–catenin, a protein recently shown to interact with Tcf/Lef transcription factors. Here, the gene encoding a Tcf family member that is expressed in colonic epithelium (*hTcf–4*) was cloned and characterized. hTcf–4 transactivates transcription only when associated with β–catenin. Nuclei of APC$^{-/-}$ colon carcinoma cells were found to contain a stable β–catenin–hTCF–4 complex that was constitutively active, as measured by transcription of a Tcf reporter gene. Reintroduction of APC removed β–catenin from hTcf4 and abrogated the transcriptional transactivation. Constitutive transcription of TCF target genes, caused by loss of APC function, may be a crucial event in the early transformation of colonic epithelium. It is also shown here that the products of mutant *APC* genes found in colorectal tumors are defective in regulating β–catenin/Tcf–4 transcriptional activation. Furthermore, colorectal tumors with intact *APC* genes were shown to contain subtle activating mutations of β–catenin that altered functionally significant phosphorylation sites. These results indicate that regulation of β–catenin is critical to APC's tumor suppressive effect and that this regulation can be circumvented by mutations in either APC or β–catenin.